IJBPAS, October, 2025, 14(10): 5708-5717

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF NOVEL MICROSPHERES OF TERBINAFINE HYDROCHLORIDE

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Received 26th April 2024; Revised 29th Aug. 2024; Accepted 21st Oct. 2024; Available online 1st Oct. 2025

https://doi.org/10.31032/IJBPAS/2025/14.10.9539

ABSTRACT

The study was aimed to formulate and evaluate microspheres of terbinafine hydrochloride by using chemical cross-linking method. Terbinafine HCl is BCS class II which has low solubility. To enhance solubility of drug with the help of PVP K30 as a carrier ratio of 1.1 ,1.2 and 1.3 using solvent evaporation technique. To achieve these objective nine formulations of microspheres were prepared. A 3^2 factorial design was employed in formulating the microspheres with Albumin and HPMC K15M as independent variables. Drug entrapment and Percentages drug release was considered as dependent variable. The prepared microspheres were characterized for their drug content, drug entrapment, percentage yield, in vitro release study. The FTIR results revealed that are is no interactions between the drug and polymers. The DSC analysis revealed that there are no interactions between the drug terbinafine hydrochloride and selected polymers. Surface morphology was studied using scanning electron microscopy (SEM). The examination of the internal structure of M5 microspheres shows that the interior of microspheres structure was solid in appearances with no pores or perforation. The microspheres were found to be spherical, quite smooth surfaces when viewed microscopically. The in vitro release studies showed that drug release was controlled (best with M5 formulation) for more than 12 h.

Keyword: Solid dispersion, Terbinafine hydrochloride, Surface morphology, BCS class II.

1. INTRODUCTION:

A controlled release medication delivery device is a device that administers medication at a fixed rate, either locally or systemic, to a specific area. This allows the medication to be localized at an active spot, resulting in more predictable and reproducible kinetics of medication release. Terbinafine Hydrochloride is an anti-fungal medication used to treat dermatophytosis, candidiasis, seborrhoea dermatitis, and onychomycosis. It remains in the nail even after a month of exposure, and the build-up subsides when tissue is replaced. Terbinafine is available in tablets and topical products, but has low oral bioavailability due to its high first-pass effect and urinary elimination. It exhibits a broad antifungal spectrum, inhibiting the conversion of squalene to ergosterol, a sterol critical to cellular integrity. Terbinafine inhibits ergosterol biosynthesis earlier than azole antifungals, which may account for its fungicidal rather than fungistatic activity **[1]**.

2. MATERIALS AND METHODS

2.1 Materials:

Terbinafine HCl was procured from Solanki Enterprises, Deccan Tower, Pune. PVP k 30, HPMC K15 M, Liquid paraffin, span 80, Glutaraldehyde obtained from Research Lab. Fine Chem., Mumbai. Egg albumin obtained from SISCO CHEM. Lab., Mumbai. All solvents and chemicals used are of analytical grade.

2.2 Methods:

2.2.1 Preparation of Solid Dispersion:

Solid dispersion of terbinafine hydrochloride was prepared by solvent evaporation method. In solvent evaporation method, the drug and carrier PVP K 30 were mixed in 1:1, 1:2 and 1:3 ratios in methanol. Solvent was allowed to evaporate in hot air oven at $45^{\circ}\pm10^{\circ}$C. The process of evaporation was opted until the constant weight was obtained. Formulation was kept in desiccator for 24 hr. The mass was pulverized and passed through sieve # 100 **[2]**.

2.2.2 Preparation of egg albumin microspheres of Terbinafine Hydrochloride:

Microspheres were prepared by using the chemical cross-linking method. In this method, solutions of albumin (having a different concentration) in 15 ml of distilled water were prepared and kept overnight. Then after 10–15-minute stirring, the solid dispersion was added to the above albumin solutions. Then above drug-polymer solutions were slowly added dropwise by injection to a beaker containing 150 ml of liquid paraffin containing 1% of span 80 as an emulsifying agent and stirred for 30 minutes at 250 RPM. The resulting microspheres were solidified using

glutaraldehyde solution and stirred for a period of 1hr. Microspheres washed with distilled water and dried at room temperature shown in **Table 1 [3]**.

3. Full factorial design

The experiments were performed with a 3^2 randomized full factorial design. In this study two factors were evaluated each at three levels, and experimental trials were performed at all nine possible combinations. The amounts of egg albumin (X_1) and HPMC k15 M (X_2) were selected as independent variables. The percentage drug entrapment efficiency and drug release were selected as dependent variable shown in **Table 1 and 2**. The data were evaluated using the Design Expert software (version 13.0.5.0), contour plot and 3D response surface graphs were plotted **[4]**.

Table 1: Formula and composition of batches.

Batch code	Solid Dispersion (mg)	Egg Albumin (mg)	HPMC k 15 M (mg)	Liquid Paraffin (ml)	Span 80 (ml)	Glutaraldehyde (ml)
M_1	250	600	80	150	1	20
M_2	250	600	90	150	1	20
M_3	250	600	100	150	1	20
M_4	250	700	80	150	1	20
M_5	250	700	90	150	1	20
M_6	250	700	100	150	1	20
M_7	250	800	80	150	1	20
M_8	250	800	90	150	1	20
M_9	250	800	100	150	1	20

4. Preformulation studies:

4.1 FTIR Spectroscopy:

FTIR spectroscopy was performed on Fourier transform infrared spectrophotometer. The spectra were scanned in the wave number range of 4000 to 400 cm^{-1}. FTIR study was carried out on drug, physical mixture of drug and polymer.

4.2 Differential Scanning Calorimetry (DSC):

Differential scanning calorimetry was performed by Differential scanning calorimeter Mettler Toledo to obtain suitable thermograms. The accurately weighed sample was placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow, at a scanning rate 300°C/min. in range of 50-350°C **[5]**.

5. Evaluation of prepared Microspheres:

5.1 Percentage yield:

The percentage yield is determined by weighing the actual amount of prepared microspheres by the total amount of all material that was used of the preparation of microspheres. The formula for calculation of % yield.

5.2 Drug entrapment efficiency:

Drug entrapment efficiency was determined by indirect method. The method utilizes filtrates of polyelectrolyte solution (i.e. liquid paraffin) from each batch. One ml of the filtrate was taken which was further diluted upto 10 ml with methanol and absorbance was taken by UV spectrophotometer at 282.1 nm **[6]**.

5.3 Drug content:

The microspheres equivalent to 50 mg of terbinafine hydrochloride were weighed accurately and crushed. The powdered microspheres were placed in 100 ml volumetric flask and the volume was made up using methanol and kept for 24 h. The solution was then filtered through Whatman filter paper. The solution was diluted with methanol and absorbance was measured at 282.1nm using UV spectrophotometer and the percent drug content was calculated.

5.4 Particle size determination:

Using optical microscopy, the microspheres particle sizes were assessed. 150 particles of each formulation were examined on an optical microscope.

5.5 In vitro dissolution studies:

In vitro release study of microspheres was performed in pH progression medium at 37°C ±0.5°C. The drug dissolution test of microspheres was performed by the paddle method (USP dissolution apparatus Type II). Microspheres equivalent to 100 mg were weighed accurately and put in 900 mL of dissolution medium. The content was rotated at 100 rpm. The pH of the dissolution medium was kept for 2 h using 0.1 N HCl. After 2 h, the pH of the dissolution medium was adjusted to 7.4 phosphate buffer and maintained up to 10 h. The samples were withdrawn from the dissolution medium at various time intervals using a pipette. The rate of drug release was analyzed using UV spectrophotometer at 282.1nm **[7]**.

5.6 Scanning Electron Microscopy (SEM):

Scanning electron microscopy has been used to determine surface morphology of prepared microspheres. The microspheres preparation was scanned randomly, and photograph were taken at appropriate magnification.

5.7 Stability studies:

Short-term stability studies on optimized formulation were carried out by storing the alginate beads at RT for 1 month period. At the end of month, the beads were examined for any physical change, changes in *in-vitro* dissolution studies [8].

6. RESULTS AND DISCUSSION:

6.1 FTIR analysis

The IR spectra of drug exhibited distinctive peaks at 2229.79 (cm^{-1}) due to C≡C stretching, 1465.95 (cm^{-1}) due to C=C stretch (aromatic ring), 2970.48 (cm^{-1}) due to C=C-H stretching, 3039.91 (cm^{-1}) due to C-H stretch (aromatic ring), 1265.35 (cm^{-1}) due to C-N stretch (aliphatic amine), 2893.32 (cm^{-1}) due to C-H stretch. These

results revealed that the drug is in pure form shown in **Figure 1 [9]**.

6.2 Differential Scanning Calorimetry

The pure drug Terbinafine Hydrochloride gives rise to a sharp peak that corresponds to melting point at 211.75ºC which indicates crystalline nature shown in figure 2. From all the studies in the characterization of Terbinafine Hydrochloride, it was concluded that the Terbinafine Hydrochloride was in pure form **[10]**.

7 Evaluation of prepared Egg albumin Microspheres

7.1 Percentage yield, Entrapment efficiency, % Drug content

The experiments were carried out and the results of % yield of albumin microspheres were 68.57% ± 0.035 to a maximum of 91.42% ± 0.06. The maximum yield was obtained with formulation M9. On further analysis of drug encapsulation of albumin microspheres, the encapsulation efficiency was found to be between 89.46±0.05 to 95.64±0.03. The % drug content of all formulation ranges between 90.91%±0.32 to 94.84%±0.30 respectively. M5 shows highest % drug content 94.84%±0.30. The mean size range of microspheres was found to be between 87±1.47 to 136±0.17 µm for all formulations. Increase in the particle size was observed with increase in polymer concentration that might be due to more viscous nature of polymer solution. The results of percentage yield, drug entrapment and drug content were shown in **Table 2 [12]**.

7.2 In-vitro dissolution study

The drug release profile of the egg albumin microspheres for the different formulation is presented in **Figure 3**. In vitro drug release studies of Terbinafine HCl microspheres were performed in 0.1 N HCL and pH 7.4 phosphate buffer in dissolution test apparatus. M1 to M9 show percentage drug release 77.04±1.26 to 90.87±1.22 at end of 12 hour. Amongst M5 was found to be the best formulation as it releases Terbinafine HCl 90.87±1.22 in a controlled manner shown in **Figure 3**.

7.3 Kinetics of Drug Release:

On the basis of best fit with the highest correlation (R^2) value, it is concluded that formulation M5 follow the zero order release kinetics. For preferred formulation M5 correlation value $R^2 = 0.9824$ shown in **Figure 4**. Drug release is mediated by diffusion through the surrounding polymeric matrices **[13]**.

8. Factorial models and counter plot and 3D Response surface plot:

ANOVA results indicated that concentration of egg albumin showed effect on % drug entrapment and % drug release. The model F-value of 13.29 and 5.17 with probability $P > 0.05$ implies that this model is significant with only a 2.93% chance that this F value could have occurred due to noise. **Figure 5** shows the contour plot of effect of egg

albumin on % drug entrapment. It represented that when the concentration of egg albumin increases then drug entrapment was found to be increasing in a microsphere. **Figure 5** shows the resulting response surface plot for % drug entrapment. It is demonstrated that the % drug entrapment depends on the concentration of egg albumin. The highest drug entrapment was obtained at optimum level of egg albumin. **Figure 6** shows the contour plot of effect of HPMC K15M on % drug release. It represented that when the concentration of HPMC K15M increases then drug release was found to be increasing in a microsphere. **Figure 6** shows the resulting response surface plot for % drug release. It is demonstrated that the % drug release depends on the concentration of HPMC K15M. The highest drug release was obtained at optimum level of HPMC K15M **[11]**.

8.1 Scanning electron microscopy:

Surface morphology was studied using scanning electron microscopy (SEM). The examination of the internal structure of M5 microspheres shows that the interior of microspheres structure was solid in appearances with no pores or perforation. The microspheres were found to be spherical, quite smooth surfaces when viewed microscopically shown in **Figure 7 [14]**.

8.2 Stability studies:

Short-term stability studies of the optimized formulation indicated that there were no significant changes in physical appearance, drug content, drug entrapment and in vitro dissolution studies at the end of one month period. The optimized formulation did not show any significant change in cumulative % drug release after 12 hr, drug content, drug entrapment when kept at normal condition **[14]**.

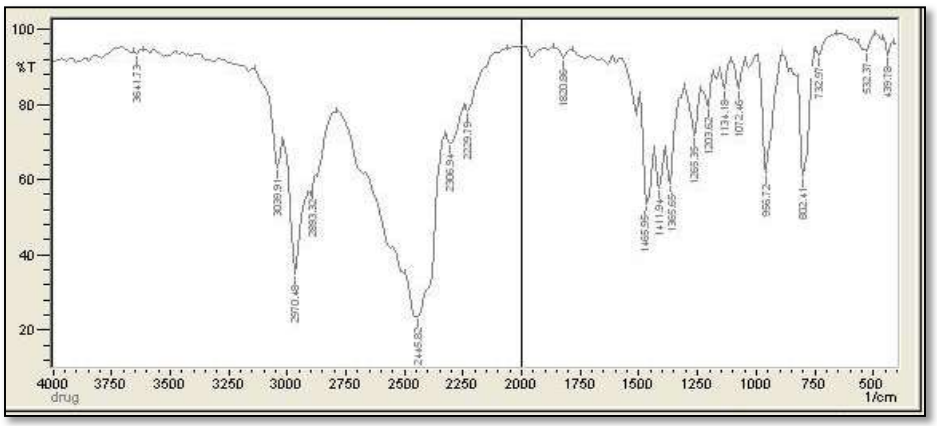

Figure 1: FTIR spectra of Terbinafine HCl

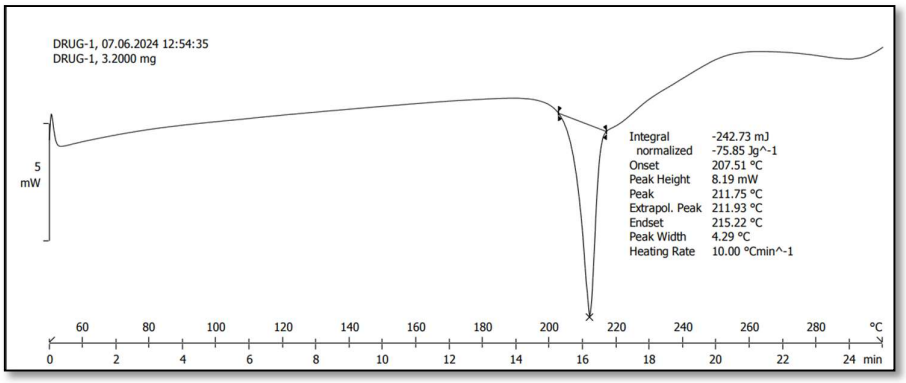

Figure 2: DSC of Terbinafine Hydrochloride

Table 2: Evaluation parameters of egg albumin microspheres

Sr. no	Batch code	Percentage yield* (%)	Entrapment efficiency (%)	% Drug content	Particle size (µm)
1	M1	68.57±0.035	89.46±0.05	90.91±0.32	94±0.10
2	M2	73.52±0.051	90.47±0.04	91.30±0.28	87±1.47
3	M3	69.69±0.045	90.30±0.05	93.07±0.02	130±1.89
4	M4	75.75±0.05	93.10±0.07	93.27±0.25	124±0.89
5	M5	82.35±0.05	95.64±0.03	94.84±0.30	132±1.13
6	M6	80.15±0.06	95.33±0.04	92.88±0.30	126±0.25
7	M7	81.81±0.041	94.65±0.03	91.70±0.23	136±0.17
8	M8	88.23±0.045	94.40±0.02	92.64±0.17	131±1.76
9	M9	91.42±0.06	95±0.06	94.25±0.10	129±1.56

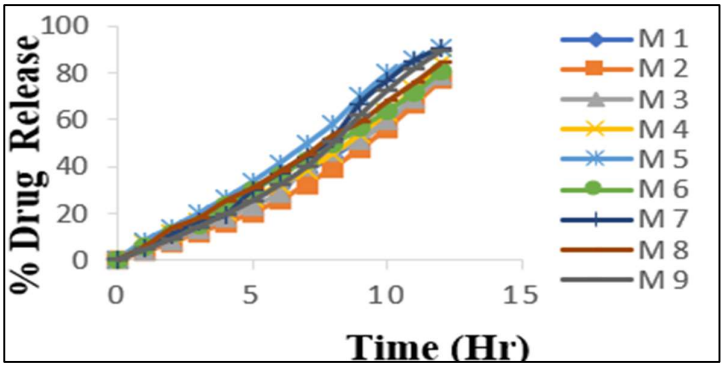

Figure 3: In vitro drug release of egg albumin microspheres

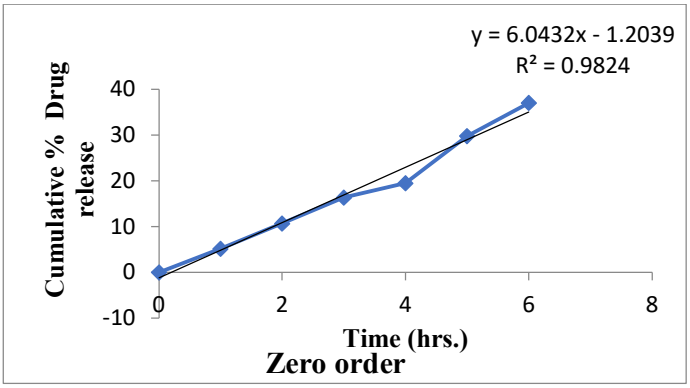

Figure 4: Zero order kinetics of M5 batch

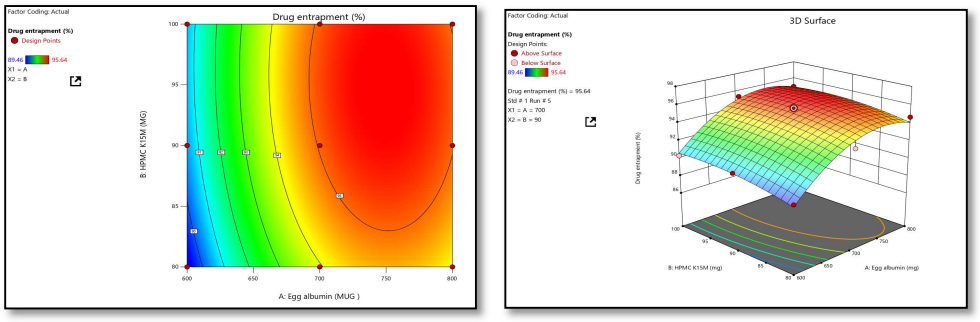

Figure 5: Contour plot and 3D Response Surface Plot show for % Drug entrapment

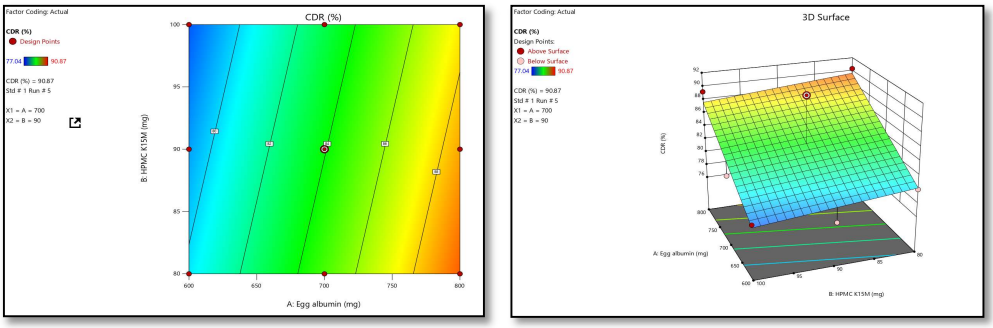

Figure 6: Contour plot and 3D Response Surface Plot show for % Drug Release

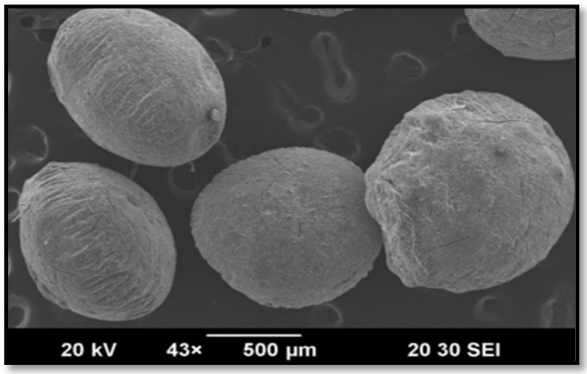

Figure 7: Scanning Electron Microphotography of Drug Loaded Microspheres

CONCLUSION:

The microspheres of terbinafine hydrochloride were successfully prepared and evaluated. The FTIR results revealed that are is no interactions between the drug and polymers. The DSC analysis revealed that there are no interactions between the drug terbinafine hydrochloride and selected polymers. Microspheres of terbinafine HCl by using egg albumin, HPMC K15 M were successfully prepared by using the chemical crosslinking method. 3^2 full factorial design was applied successfully. The concentration of the polymer influenced the drug entrapment efficiency as well as the in vitro release. The in vitro release studies showed that drug release was controlled (best with M5 formulation) for more than 12 h. Surface morphology was studied using scanning electron microscopy (SEM). The

microspheres were found to be spherical and quite smooth surfaces when viewed microscopically. The present study signifies the utility of microspheres in retarding the drug release. This may, in turn, reduces the frequency of dosing, thereby improving the patient compliance. So, from this, it could be concluded that the prepared microspheres can be used for the controlled drug delivery of the drug.

ACKNOWLEDGEMENT:

Authors are thankful to Navsahyadri Institute of Pharmacy, Pune, for providing necessary facilities to carry out this work. Would like to thank our guide Miss Pooja Kashid, Mrs. Trushali. A. Mandhare who took her valuable time to guide us throughout the process.

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